

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: JEREMY M. BEN-DAVID & CO. LTD. P.O. BOX 45087 HAR HOTZVIM HI-TECH PARK JERUSALEM, ISRAEL 91450		16 - 9 - 2005 RECEIVED 22201		Date of mailing (day/month/year) 01 SEP 2005	
Applicant's or agent's file reference NEU202-12.2		FOR FURTHER ACTION See paragraph 2 below			
International application No. PCT/IL04/00330		International filing date (day/month/year) 15 April 2004 (15.04.2004)		Priority date (day/month/year) 29 April 2003 (29.04.2003)	
International Patent Classification (IPC) or both national classification and IPC IPC(7): A61K 43/64; 31/405 and US Cl.: 514/343, 415					
Applicant NEURIM PHARMACEUTICALS (1991) LTD.					

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Sreenivasan Padmanabhan Telephone No. 703-308-1235
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Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/IL04/00330

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing
☐ contained in international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IL04/00330

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-21	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-21	NO
Industrial applicability (IA)	Claims 1-21	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1-21 meet the criteria set out in PCT Article 33(2), because the prior art does not teach or fairly suggest a pharmacologically active combination having utility in treating insomnia patients, which comprises melatonin and nicotine or the method of alleviating impairment of cognition with the combination of melatonin and nicotine.

Claims 1-21 lack an inventive step under PCT Article 33(3) as being obvious over Myers et al. (US 6,486,172 B2) in view of Oxenkrug et al. (US 6,353,015 B1).

Myers et al. teach nicotine increase cognition and attention. (column 17, lines 30-34).

Myers et al. do not teach the enhancement of cognition with combination of nicotine and melatonin.

Oxenkrug et al teach melatonin improve cognition and protect against neurotoxicity. (column 12, lines 20-25).

It would have been obvious to one of ordinary skill in the art to formulate a pharmaceutical composition comprising nicotine and melatonin because each of the active agents are taught to be effective in enhancing cognition. One would have been motivated to combine nicotine and melatonin in a single composition with a reasonable expectation of successfully improving cognition in a convenient single formulation.

Claims 1-21 meet the criteria set out in PCT Article 33(4), since the pharmacologically active combination having utility in treating insomnia patients, which comprises melatonin and nicotine or the method of alleviating impairment of cognition with the combination of melatonin and nicotine have an industrial applicability in pharmaceutical art.

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From the INTERNATIONAL SEARCHING AUTHORITY

To:
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P.O. BOX 45087 HAR HOTZVIM
HI-TECH PARK
JERUSALEM, ISRAEL 91450

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference NEU202-12.2	Date of mailing (day/month/year) 01 SEP 2004
International application No. PCT/IL04/00330	International filing date (day/month/year) 15 April 2004 (15.04.2004)
Applicant NEURIM PHARMACEUTICALS (1991) LTD.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Sreenivasan Padmanabhan <i>Janie Ford</i> Telephone No. 703-308-1235
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Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)